"STUDY OF SOME MEDICINAL PLANTS FOR ANTI-DIABETIC EFFECT AND ITS COMPLICATIONS.''

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SR.NO.	CONTENT	PAGE NO
01.	ABSTRACT OF PROPOSED WORK PLAN	03
02.	INTRODUCTION	4-5
03.	REVIEW OF LITERATURE AND DEVELOPMENT IN THE SUBJECT	6-9
04.	OBJECTIVES OF RESEARCH	10
05.	METHODOLOGY TO BE ADOPTED	11-12
06.	IMPORTANCE OF STUDY	13-14
07.	PROPOSED WORK PLAN	15
08	REFERENCES	17-19

ABSTRACT

Diabetes mellitus has become a major public health and economic problem across the globe. The inadequacies, as well as serious adverse effects associated with conventional medicines, led to a determined search for alternative natural therapeutic agents.

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high level of glucose in the blood resulting from a relative or absolute deficiency of insulin action. DM affects a population of approximately 424.9 million adults (aged 20-79) worldwide in 2017. This disease is associated with micro and macro vascular complications which lead to the development of disability and life-threatening medical conditions. Hyperglycemia, hyperlipidemia, and oxidative stress are the main important characters of DM and represent a major risk factor for the development of complications of diabetes.

To date, the available therapy for diabetes includes insulin and various oral antidiabetic agents such as sulfonylureas, thiazolidinediones, and α-glucosidase inhibitors. These drugs are used as monotherapy or in combination to achieve better glycemic control. Good glycemic control delays the development or progression of diabetic complications but does not completely restore diabetic complications. Anti diabetic drugs is associated with a number of serious adverse effects. Therapeutic alternatives comprised of antihyperglycemic, antihyperlipidemic, and antioxidant activities with proven long-term safety should be targeted in a clinical setting for patients with coexisting diabetes and metabolic disorders. Hence, ant diabetic discovery has shifted its focus to medicinal plants to offer new promising efficient drugs with minimal adverse effects and lower costs. Natural products play a major role in the discovery of new therapeutic agents and have received much attention as sources of bioactive substances including antioxidants, hypoglycemic agents. With this view present study is aimed for **"STUDY OF SOME MEDICINAL PLANTS FOR ANTI-DIABETIC EFFECT AND ITS COMPLICATIONS."**

SECTION 01

INTRODUCTION

Diabetes mellitus is a global public health problem all over the world. According to a widely accepted estimation, the number of diabetic patients would reach 366 million by the year 2030**.** Cancer is one of the most dreaded diseases of the 20th century and spreading further with continuance and increasing incidence in 21st century. Diabetes mellitus (DM) is a major cause of avoidable blindness in developing and developed countries. Patients with Diabetes mellitus (DM) are 25 times more likely to become blind and other related systemic order than non-diabetics.1 Diabetes mellitus has emerged as a major public health problem in India. The first authentic data on the prevalence of diabetes in India came from the multi-centric study conducted by Indian Council of Medical Research (ICMR) in the early services. [4]

Currently, 40.9 million Indians are estimated to be suffering from diabetes. By 2025, this number will rocket to 69.9 million, and potentially 85 million by 2030. In addition, 35 million Indians are at risk for diabetes. The International Diabetes Federation has come up with much higher figures in a recent report estimated that in 2011, 366 million people worldwide had Diabetes mellitus (DM) and if this trend continues, by 2030, 552 million people i.e. one in ten adults will have Diabetes mellitus. [7]

In the treatment of Diabetes Mellitus measures transformation in lifestyle along with appropriate diet and weight control remains critical component treatment. Along with this Dietary management includes the use of traditional medicines that are mainly derived from herbal plants. Even now approximately 60-85% of the world population is almost entirely dependent upon traditional medicines. Indian plants which are most effective and the most commonly studied in relation to diabetes and their complications are such as *Allium Sativum* (Garlic), *Azadirachta Indica* (Neem), *Ocimum Santum* (Tulsi), *Ficus bengalenesis, Gymnema sylvestre, Momordica charantia.* [10].

Given a reasonable likelihood that medicinal plants with a long history of human use will ultimately yield novel drug prototypes, systematic and intensive search in plants for new drugs to treat diabetes mellitus seem to be of great utility. This approach seems likely to increase the chances for discovering new drugs for the management of diabetes mellitus.

In view of above present study is envisaged to screen some medicinal plant extracts for its effectiveness in Diabetes Mellitus along with its protective effects against Diabetic complications.

SECTION 02

REVIEW OF LITERATURE AND DEVELOPMENT IN THE SUBJECT (PREVIOUS WORK DONE IN THE RELEVANT AREA)

- Ameur Ben Younes et al (2018) has reported that Phytochemical Screening and Antidiabetic, Antihyperlipidemic, and Antioxidant Properties of *Anthyllis henoniana* (Coss.) Flowers Extracts in an Alloxan-Induced Rats Model of Diabetes.

- Naheed Akhtar et al (2018) in this study revealed that antidiabetic activity of *Ipomoea batatas* L. extract in alloxan-induced diabetic rats. They show that significantly decrease in glucose level in rat.

- Sudhanshu Kumar Bharti et al (2018) in this review reported that Most of the plants having antihyperglycaemic activity also show other functions that are beneficial to patients with DM. They provide a lead with respect to diabetes management, showing the regulatory effects on various steps of different metabolic pathways that may have therapeutic and other applications.

- Cesaire Feudjio *et al (2018)* studied that the administration of *Phragmanthera capitata* extract causes a significant fall of basic glycaemia of the normoglycemic, temporary hyperglycemic and diabetic rats. This extract contains saponins, flavonoides, tannins, steroids and terpenes. Some flavonoides like quercetins have the capacity of increasing secretion of insulin by pancreatic β cells. The administration of *Phagmanthera capitata* extract to diabetic rats significantly decreased hyperglycaemia.

- Manal Mortady Hamed (2018) reported that It is a significant effort to isolate and clarify their pharmacological mechanism, and lastly, to create traditional dosage forms which controls and developed diabetes as well as takes care of associated complications.

- Hau Van Doan et al (2018) in this study revealed that antidiabetic activity of C. cainito stem bark with possible modes of action, glucose uptake stimulation and α-glucosidase inhibitory effect. the extract at 500 mg/kg significantly reduced the area under curve of blood glucose level in oral glucose tolerance test in normal mice. In alloxan-induced diabetic model was reported.

- Samuel Odeyemi et al (2018) in this review compare the families of previously reported anti-diabetic plants in the Eastern Cape by rating the anti-diabetic activity, mode of action and also highlight their therapeutic potentials based on the available evidence on their pharmacology and toxicity. All the investigated plants also inhibit oxidative stress as part of their hypoglycemic activity with less toxicity. This provides a resource to enable thorough assessments of the therapeutic profiles of available medicinal plants used for the management of diabetes.

- A.W. Siddiqui et al (2018) aqueous extracts of S. cumini and G. sylvestre (200 mg/kg) decrease the blood glucose levels in STZ diabetic rats. Study indicates that the aqueous extracts of S. cumini and G. sylvestre exhibited activity both in normal and streptozotocin-induced diabetic rats and also increased the tolerance of animals on oral glucose tolerance test.

- Nishi Saxena et al (2018) in this study revealed that Herbal formulation was prepared with the mixture of alcoholic extract of *Tribulus terrestris* fruits, *Boerhavia diffusa* roots and *Azadirachta indica* leaves. Antidiabetic activity using 100 mg/kg and 200 mg/kg of formulation was studied in streptozotocin induced diabetic albino Wistar rats. The dose of 200 mg/kg had better effect than the standard drug glibenclamide. The herbal formulation is a potent antidiabetic and safe for use.

- Narhe Sonal et al (2018) reported that focus mainly on diabetes, plants such as *coccinia indica, Tragia involucrate, G. sylvestre, Pterocaprus marsupium, T. foenum-graceum, Moringa oleifera* used as anti-diabetic in various traditional medicines, constituents like saponins, flavonoides, tannins, steroids

and terpenes. Some flavonoides isolated from these plants, various mechanism through which herbs act against diabetes and few examples of anti-diabetic formulation available in the market.

- Paul C. Chikezie et al (2018) reported that Several species of medicinal plants used for the management of DM worldwide have been evaluated. Some of theplants include: *Allium cepa* (Onion), *Allium sativum* (Garlic), *Aloe vera*, *Cinnamomum cassie*. Some plants shows polysaccharides, sterols, terpenoids, alkaloids, saponins, flavonoids, amino acids and their derivatives are the most encountered bioactive principles that exhibited glycemic control in experimental animals.

- Hasani Prabodha Sudasinghe et al (2018) their study investigated the in vivo ability of P. suberosa leaves to manage blood sugar status and associated cholesterol levels. Phytochemical screening revealed the presence of alkaloids, unsaturated sterols, triterpenes, saponins, flavonoids, tannins and proanthocyanidins. Carbohydrate content of the leaves was 12.97%. The maximum hypoglycemic effect was observed after 4 h of 50 and 100 mg/kg ALE administration.

- P. Swaroopa et al (2017) some plants having anti diabetic property. Although many plants are recommendation, further pharmacological and chemical research should be done to elucidate the exact mechanism of hypoglycaemic activity. Herbal drugs have effect on protecting cells and smoothing out fluctuation in glucose levels. there is very little biological knowledge on the specific modes of action in the treatment of diabetes, but most of the plants have been found to contain substances like glycosides, alkaloids, terpenoids, flavonoids etc. that are frequently implicated as having anti diabetic effects

- Prabhakar Kumar Verma, et al (2017) in this study revealed that Phytochemical Evaluation and Antidiabetic Potential of Trichosanthes Dioica Roxb. in Streptozotocin Induced Diabetic Rats.

- Tafesse et al (2017) has reported that Antidiabetic activity and phytochemical screening of extracts of the leaves of Ajuga remota Benth on alloxan-induced diabetic mice.

- Jawaid T., *et al* (2014) has reported that Pumpkin seed extract having anti diabetic, antitumor, antibacterial and anticancer activity. It has also found to have strong hypotriglyceridemic and serum cholesterol lowering effect.

- Chitra Jain et al., (2014) in this study revealed that Anti-diabetic potential of flavonoids and other crude extracts of stem bark of *Mangifera indica* Linn: A comparative study.

Extensive literature survey reveals numbers of medicinal parts are claimed in traditional system for its effectiveness in metabolic disorder like Diabetes. Many plants just evaluated for their preliminary activity but not for their extensive screening including that for its complication. Accordingly the present study design with an objective to explore the anti-diabetic activity of some herbal plants.

SECTION 03

OBJECTIVES OF RESEARCH

In this modern era for primary health care, most of the world populations still use herbal medicine because of its better cultural acceptability, better compatibility with the human body, and lesser side effects. Diabetes is a common disease that is rising in prevalence worldwide with the highest prevalence in industrialized countries. Diabetes affects about 300 million people worldwide and it has been estimated that a further 100 million will be affected by 2025. Literature survey reveals that plants have always been proven as a better source of drugs and when it comes to treatment of diabetes. Hence, it was thought worth to undertake this study to screen anti-diabetic activity. [13]

With an objectives -

- Extraction of plant material using proper solvent.
- *In-vitro* antioxidant activity of plants extract.
- Acute oral Toxicity study of plants extract.
- Preclinical Pharmacological evaluation of plants extract for Anti-diabetic effect and its complication.
- Development of suitable Formulation.
- Stability studies of developed formulation.

SECTION 04

METHODOLOGY TO BE ADDOPTED

1. **Collection and authentication of plant material:**

   The whole plant or its parts will be collected from the known sources. The sample will get identify and authenticate by the botanist of region.

2. **Processing of plant material:**

   Collected plant material will be subjected to processing such as drying, grinding, sieving etc as per official standards.

3. **Pharmacognostic evaluation of plant material:**

   Whole plant or its parts will be subjected to Pharmacognostic evaluation for Morphological Evaluation and Microscopic evaluation and powder characteristics.

4. **Extraction of plant material with various solvents:**

   Coarse powder form of plant material will be subjected to successive extraction. The solvent & extraction method will be decided according to chemical constituents & its nature.

5. **Phytochemical investigation of plants extracts:**

   Phytochemical investigation of extract will be carried out by qualitative chemical test and chromatographic technique.

6. **Pharmacological Screening of Formulation:**

   1. **Acute toxicity study**

      For the determination of safe dose of extract will be subjected for the acute toxicity according to OECD guidelines.

   2. **Evaluation of in-vitro antioxidant activity.**

      The antioxidant activity of extract will be assessed with help of *in-vitro* tests

   3. **Evaluations of anti-diabetic activity of extract.**

      i. The extract will be subjected for study of anti-diabetic activity by Alloxan induced and or Streptozotocin induced diabetic animal model as per reference standard methods.

ii. Diabetic complication against hepatic and nephropathy complications will be carried out in diabetes induced animal model.

7. Development of suitable Formulation.

8. Stability studies of developed formulation.

SECTION 05

IMPORTANCE OF STUDY/ SOCIETY APPLICATION

Diabetes mellitus (DM) is the most common endocrine disorder resulting from a defect in insulin secretion, insulin resistance or both. It is the third leading cause of morbidity and mortality, after heart attack and cancer. In 2015, about 415 million people had diabetes in the world and 78 million people in the Southeast Asia (SEA) region; by 2040 this will rise to 140 million. India is one of the epicentres of the global DM pandemic. There were 69.1 million cases of diabetes in India. [13]

The increasing medical burden on patients with diabetes-related complications also results in an enormous economic burden, which could severely impair global economic growth in the near future. This shows that today's health system has conventionally been poorly equipped to confront the mounting impact of diabetes on a global scale and demands an urgent need for newer and better options. The overall challenge of this field of diabetic treatment is to identify the individualized factors that can lead to improved glycemic control. [13]

Nearly 8–10% of the world population suffers from diabetes. The synthetic drugs produce side effects. Besides conventional oral and injectable medications, diabetes treatments include diet modification, regular exercising, lifestyle changes, weight regulation and other alternatives or add on therapies such as herbal therapy. Therefore, there is a dire need to identify new herbal plants to treat diabetes. Herbal drugs are prescribed widely as drugs of choice because of their effectiveness, few side effects and relatively low cost. Herbal medicines are being used by nearly about 85% of the world population, primarily in developing countries for primary health care. Current status of health care system in adequacies of synthetic drugs is likely to be more intensive in the coming years. It has been reported that there has been horrible increase use of traditional herbal medicine to overcome the diseases and disorders caused due the synthetic drugs. [21]

According to World Health Organisation (WHO) estimates 415 million people suffer from Diabetes, 1.6 million people died in 2016. In India, an estimated that 346,000 deaths were attributed to Diabetes in 2015 (WHO 2015) and it was seen as

one of the leading cause of morbidity and mortality in rural India. India has a rich cultural heritage of traditional medicine.

As per the International Diabetes Federation (2013), approximately 50% of all people with diabetes live in just three countries: China (98.4 million), India (65.1 million) and the USA (24.4 million). It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is changing into an epidemic in many low and middle-income countries. Diabetes is certain to be one of the most challenging health problems in the 21st century. [15]

Hence plants have been suggested as a rich, as yet unexplored source of potentially useful ant diabetic drugs. Many traditional herbal treatments for diabetes are used throughout the world. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic one.

The multiple therapeutic action and uses of these drugs are sufficiently described in classical literature on indigenous medicines in many medicinal plant books. It is a disease that does not have the boundaries of age, race and gender. The availability of effective medications is not withstanding with present challenges and the prevalence of Diabetes is continuously increasing with time. Moreover the side effects of these drugs are also quite disturbing. Hence there is an increasing demand for use of traditional herbal drug. As existing therapies for the treatment of the diabetes are not complete and satisfactory due to major side effects at higher doses and prolonged treatment, present scenario necessitate new treatment. Selected plant and its parts is less explored but is reported to possess important phytoconstituents of wide range which will be useful in Diabetes. Such constituents can be evaluated using modern tools for analytical, pharmacological and toxicological profile. Present project may help to explore novel constituents for the mentioned pathologies which could be more effective as well as associated with lesser side effect which will be beneficial for the society. With this regards present project is undertaken with objectives to identify, active constituents present in the selected medicinal plants and to evaluate its ant diabetic activity.

SECTION 06

PROPOSED WORK PLAN

1. Collection, Identification and Authentication of selected Medicinal Plant material.

2. Processing of crude drug

3. Pharmacognostic evaluation of plant material

a) Morphological Evaluation

b) Microscopic evaluation and powder characteristics

4. Extraction of plant material:

a) Selection of Extraction method

b) Selection of Solvent

5. Phytochemical investigation of plants extracts:

Phytochemical investigation of extract will be carried out by qualitative chemical test and chromatographic technique

6. Pharmacological Screening of plant extracts for:

i) Safe dose calculation by acute oral toxicity studies and repeated dose toxicity study.

ii) Pharmacological screening for antioxidant activity.

iii) Anti-diabetic and Diabetic Complication study.

7. Development of suitable Formulation.

8. Stability studies of developed formulation.

9. Interpretation of data and its presentation

YEAR WISE PLAN OF WORK AND TARGET TO ACHIEVE

Present study is designed in such a way that it will come to a conclusive outcome within 03 years from the date of Allocation. The year wise plan includes**.**

YEAR 01

Literature survey, Plant Collection and preliminary screening, Morphological and Microscopic evaluation, Drying, Powdering, Physical evaluation of powdered drug.

YEAR 02

Extraction of the Plant material by suitable method of extraction, phytochemical evaluation of extracts/ fractions by different qualitative and quantitative methods of evaluation (as per WHO guidelines). *In vitro* Pharmacological screening of different extracts for anti –oxidant activity

YEAR 03

In vivo screening of anti -diabetic activity of extract on suitable animal model and by evaluating various parameters. The active components present in the extract which will show maximum promising anti-diabetic effect, Development of suitable Formulation, Stability studies of developed formulation, Compilation, interpretation of data and thesis writing.

SECTION 07

REFERENCES

1. Mishra Shanti Bhushan, Rao Ch. V., Ojha S.K, Vijayakumar m., Verma a. 'An analytical review of plants for antidiabetic activity with their phytoconstituent & mechanism of action' *IJPSR* (2010), Issue 1, Vol.1.

2. Mohamed Bnouham Abderrahim Ziyyat, Hassane Mekhfi, Abdelhafid Tahri, Abdelkhaleq Legssyer 'Medicinal plants with potential Antidiabetic activity - A review of ten years of herbal medicine research (1990-2000)' *Int J Diabetes & Metabolism* (2006) 14: 1-25.

3. Najma Sultana *'invitro* hypoglycemic activity of methanolic extract of some indigenous plants' 2007.

4. Kaushik M, Jaiswal A, Shah N, Mahal A: High-End Physician emigration from India. Bulletin of the World Health Organization 2008, 86(1):40-40

5. Shradha Bisht, S.S.Sisodia, 'Anti-Hyperglycemic And Antidyslipidemic Potential Of *Azadirachta indica Leaf* Extract In STZ- Induced Diabetes Mellitus' *J. Pharm. Sci. & Res*. Vol.2 (10), 2010,622-627.

6. K. Kadhirvel, P. Rajivgandhi, G. Narayanan, V. Govindaraji, K. Kannan, R. Vanithaselvi, S. Ramya and R. Jayakumararaj. 'Investigations on Anti-Diabetic Medicinal Plants Used by Tribal Inhabitants of South India' *Ethnobotanical Leaflets* 14: 236-47, 2010.

7. N.H. Cho , J.E. Shaw , S. Karuranga. 'IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045'. Diabetes research and clinical practice 138 (2018) 271 – 281.

8. Salau B. A, Ajani, E. O, Akinlolu, A. A, Ekor, M. N and Soladoye M. O 2010. Methanolic Extract of Musa Sapientum Sucker Moderates Fasting Blood Glucose and Body Weight of Alloxan Induced Diabetic Rats. *Asian J. Exp. Biol. Sci. , Vol 1(1):30-35.*

9. Santosh Kumar Singh, Achyut Narayan Kesari, Prashant Kumar Rai and Geeta Watal 2007. Assessment of glycemic potential of musa paradisiaca stems juice. Indian Journal of Clinical Biochemistry, 22 (2) 48-52.

10. Goyal S., Ramawat K.G. 'The Indian Herbal Drugs Scenario in Global Perspectives' Bioactive Molecules and Medicinal Plants.2008 :323-345.

11. Ojewole JA, Adewunmi CO. Hypoglycemic effect of methanolic extract of Musa paradisiaca (Musaceae) green fruits in normal and diabetic mice. Methods Find Exp Clin Pharmacol. 2003 Jul-Aug; 25(6):453-6.

12. Chhanda Mallick, Kausik Chatterjee, Mehuli Guha Biswas and Debidas Ghosh 2007. Antihyperglycemic effects of separate and composite extract of root of *Musa paradisiaca* and leaf of *Coccinia indica* in streptozotocin-induced diabetic male albino rat. *Afr. J. Trad. CAM* 4 (3): 362 – 371

13. S K Bharti, Supriya Krishnan, Ashwini Kumar and Awanish Kumar. 'Therapeutic Advances in Endocrinology and Metabolism. 2018, Vol. 9(3) 81–100

14. Grover JK, Yadav S, Vats V 2002: Medicinal plants of India with anti-diabetic potential. J Ethnopharmacol 81: 81-100.

15. Jaya Prasad Tripathy1 , J. S. Thakur. 'Prevalence and risk factors of diabetes in a large community-based study in North India: results from a STEPS survey in Punjab, India. Diabetol Metab Syndr (2017) 9:8

16. Behzad Moradi, Saber abbaszadeh,mohsen alizadeh 2018: The most useful medicinal herbs to treat diabetes.Biomedical research & Therapy,5(8);2538-2551.

17. Unnikrishnan R, Anjana RM and Mohan V. Diabetes mellitus and its complications in India. *Nat Rev Endocrinol* 2016; 12: 357–370.

18. Mayank Kumar, Shashi Alok, Sanjay Kumar Jain and Amita Verma. Antidiabetic Activity of Plants with Their Phytoconstituents: A Review, *IJP, 2014; Vol. 1(1): 9-22.*

19. Chitra Jain, Archana Singh, Padma Kumar, Keerti Gautam. Anti-diabetic potential of flavonoids and other crude extracts of stem bark of *Mangifera indica* Linn: A comparative study. Journal of Scientific and Innovative Research 2014; 3 (1): 21-27.

20. Nitesh Pradhan, Abhishek Sachdeva, Tushar Goel, Sahil Arora, Shekhar Barua. Prevalence of diabetes mellitus in rural population of Mullana, district Ambala, Haryana, India. *Int J Res Med Sci. 2018 Apr; 6(4):1248-125.*

21. Poornima M. P., Padmaja R. Walvekar. Prevalence of type 2 diabetes mellitus among adults aged between 30 to 60 years residing in rural area: a cross sectional study. *Int J Community Med Public Health. 2018 Aug; 5(8):3639-3642.*

22. Rana MS, Samant SS. 2011 a. Diversity, indigenous uses and conservation status of medicinal plants in Manali wildlife sanctuary, north western Himalaya. Indian J Trad Knowl. 10:439–459

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